REMARKS

In the Office Action dated December 31, 2007, claims 1-31 are pending. Claims 8, 9, 11-13, 15, 26-28, 30 and 31 are objected to as improper multiple dependent claims and are not further examined. Claims 1-7, 10, 14, 16-25 and 29 are examined and are rejected. The Examiner also indicates that the listing of references cited in the Search Report issued in PCT/AU2003/001497, is not a proper information disclosure statement (IDS).

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Information Disclosure Statement

Applicants filed an Information Disclosure Statement (IDS) on May 2, 2008, citing references listed in the International Search Report issued in PCT/AU2003/001497, and providing copies of the non-patent documents. As such, the Examiner's objection with respect to IDS is overcome. Withdrawal thereof is respectfully requested.

Claim Amendments

Independent claims 1, 2 and 17 have been amended such that the claimed methods involve co-localizing mitochondrial DNA and detecting the levels of the co-localized mitochondrial DNA. Support for such amendment is found in the specification and in original claim 12, for example. Further, claims 1, 2 and 17 have been amended to further delineate the diseases in respect of which the relevant method is to be performed. Support for this amendment is found in original claims 5 and 7, for example. Claims 3-4, 6-12, 14, 18-19, 21-27 and 29 have been canceled without prejudice. No new matter is introduced by the foregoing amendments.

Claim Objections

Claims 8, 9, 11-13, 15, 26-28, 30 and 31 are objected to as improper multiple dependent claims. Claims 4 and 7 are objected to for reciting limitations not consistent with the base claims from which claims 4 and 7 depend.

These objections are overcome by the foregoing amendments to the claims. Withdrawal of the objections is therefore respectfully requested.

35 U.S.C. §112 – Indefiniteness

Claims 1-7, 10, 14, 16-25, and 29 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Specifically, the Examiner has rejected claims 1, 2-7, 10, 14, 16, 17-25 and 39 over the recitation of "the subject nucleic acid regions derived from" a sample for lacking antecedent basis. Applicants respectfully submit that the claims, as amended, are drawn to analyzing mitochondrial DNA. It is believed that the amendments to the claims have overcome the Examiner's rejection in this regard.

The Examiner has also objected to claims 2-7, 10, 14, 16, 17-25 and 39 over the recitation "for diagnosing and/or monitoring a clonal population of cells". According to the Examiner, there is not a nexus between the purpose of the method as recited in the preamble and the required methods steps. Applicants respectfully submit that from the claim language, it would be clear to one of skill in the art that a clonal population of cells is monitored based on detecting the level of co-localisation of mitochondrial DNA. Therefore the claims are not vague, contrary to the Examiner's allegation.

Further, the Examiner has objected to claims 4, 5, 7, 14, and 16 over the phrase "corresponds to", used in reference to the relationship between cells and a disease. It is noted

that the claims, as amended, reference specific disease conditions and have used the phrase "characteristic" instead of "corresponds to". It is believed that the claims, as amended, are not indefinite.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

35 U.S.C. §102(b) – Novelty

Claims 1-5, 17-20, 23, 24 are rejected under 35 U.S.C. §102(b) as anticipated by Greiner et al. (*Am. J. Pathol.* 146: 46-55, 1995) ("Greiner"). Greiner teaches the analysis of clonality of T cells in the leukemias using PCR and denaturing gradient gel electrophoresis (DGGE).

Applicants respectfully submit that the claims as amended are now directed to screening for mitochondrial DNA. Greiner does not teach detecting co-localized mitochondrial DNA, as presently claimed. Therefore, the §102(b) rejection based on Greiner is overcome, and withdrawal thereof is respectfully requested.

35 U.S.C. §103(a) -Obviousness

Claims 6, 7, 21, and 22 are rejected under 35 U.S.C. §103(a) as unpatentable over Greiner in view of Gilliand et al. (1991). Claims 10 and 25 are rejected under 35 U.S.C. §103(a) as unpatentable over Greiner in view of Enright et al. (2000). Claims 14, 16, and 29 are rejected under 35 U.S.C. §103(a) as unpatentable over Greiner in view of Nomoto et al. (2002).

Applicants respectfully disagree with the Examiner's rejections. It is noted that the claims, as presently amended, are directed to methods based on co-localizing mitochondrial

DNA and detecting the levels of the co-localized mitochondrial DNA. The cited references, taken alone or in combination, simply do not teach or suggest the presently claimed methods.

Primary Reference to Greiner et al. (1995) ("Greiner")

This document teaches analysis of the clonality of T cells in leukaemia using a combination of PCR and denaturing gradient gel electrophoresis, which is directed to analyzing TCR-γ rearrangements. The Examiner regards this disclosure as broadly teaching the method of the present invention.

In the first instance, it should be noted that although Greiner has examined co-localisation of TCR-γ DNA in order to identify differences in rearrangement patterns between clones, this is, in fact, significantly different from the notion of screening for mitochondrial DNA mutations. That is, the choice of the region of DNA to be examined is not merely an issue of choosing any one DNA region over another based on the fact that some level of change to the germline sequence has been observed to occur. Rather, and as detailed quite specifically in the specification, the regions of DNA that are the subject of analysis by virtue of the method of the present invention are those in which acquired mutations occur at the time that the descendants of an ancestral cell divide to form new daughter cells. See page 11, lines 4-25, and page 17, line 6 to page 18, line 1 of the specification. In the context of an explanation provided in the specification in relation to the "diagnostically distinctive DNA region", it is clear that the notion of rearranged T-cell and B-cell gene sequences does not fall within the scope of a "diagnostically distinctive DNA region" as defined in the present application, since T-cell and B-cell gene rearrangements are germline gene rearrangements, which are made at the time of commitment of a stem cell to a B or T cell lineage and are stably carried from one generation of daughter cells to the next. DNA gene rearrangements of T cell receptors or immunoglobulin receptor genes are

therefore not acquired mutations of the type that are defined by the present specification and that occur in the context of mitochondrial DNA.

Accordingly, although Greiner also employs the technology of co-localizing a DNA population in order to determine whether there is a representative band indicating a clonal population of cells which express an identical DNA region sequence of interest, it is the specific nature of the sequence which is selected to be analyzed that is, in part, where the invention lies in the context of the present application. As presently claimed, Applicants have defined the mitochondrial DNA region as the region to be analyzed. Greiner simply does not teach or remotely suggest analyzing the mitochondrial DNA region as the basis for identifying a clonal population of cells. This fundamental deficiency of Greiner is not cured by any of the secondary references.

Secondary Reference to Gilliland et al. (1991)("Gilliland")

The authors of this reference employed an adapted PCR technique for analyzing clonality at a specific gene linked to the X chromosome. Gilliland does not teach or suggest the technique of co-localisation of DNA, which is an essential feature of the present claims. Gilliland performed Southern Blot analysis, which required the design and use of sequence-specific probes, this being a significant problem which the present invention has overcome.

Further, Applicants respectfully submit that Gilliland does not teach or suggest characteristics of acquired mutation development in mitochondrial DNA, or the notion of using co-localization of DNA as a means of identifying the existence of clones exhibiting a common sequence. Therefore, Applicants respectfully submit that Gilliland does not provide any teaching relevant to the presently claimed invention. The rejection of claims 6, 7, 21, and 22 under 35

U.S.C. §103(a) as unpatentable over Greiner in view of Gilliand (1991) is improper. Withdrawal of the rejection is therefore respectfully requested.

Secondary Reference to Enright et al. (2000) ("Enright")

This particular article discloses the analysis of clonal populations of microorganisms and is cited in combination with Greiner against claims 10 and 25.

Applicants respectfully submit that the rejection of claims 10 and 25 is moot in view of the cancellation of these claims. Withdrawal of the rejection is therefore requested.

Secondary Reference to Nomoto et al. (2000) ("Nomoto")

Although the Examiner notes that this article teaches the analysis of several polymorphic loci of the mitochondrial D loop DNA, this article does not disclose the analysis of acquired mitochondrial DNA mutations via a co-localization-based technique. In fact, this article, although disclosing analysis of mitochondrial DNA in solid tumors, was focused on probing mitochondrial DNA for specific gene mutations that are known to be associated with hepatocellular carcinoma onset. That is, Nomoto's study was directed to a disease condition characterized by specific nucleotide substitutions, and therefore, the diagnosis of hepatocellular carcinoma in a patient required actual sequencing of the D loop region of the mitochondrial DNA in order to determine whether the patient expressed the specific substitution that is characteristic of that disease condition. Specifically, from Figure 1 of Nomoto, it is clear that the authors have used sequencing to identify the specific DNA mutations of T→C, C→T and G→A. These specific mutations are only relevant to this specific carcinoma type (hepatocellular carcinoma), and are not characteristic of any other type of neoplasm.

The present invention, however, is based on the fact that knowledge of the DNA sequence or of the presence or absence of a specific mutation in a particular gene is not required. That is, on the basis of the mechanism by which acquired mitochondrial DNA mutations occur from an ancestral cell through to the ongoing generations of daughter cells, it is not necessary to have *any* information of the DNA sequence other than to know that in light of the fact that mitochondrial DNA has been found to exhibit these acquired mutations, these occurring across all cell types and not just diseased cell types, it is possible to identify the existence of a clonal population without any knowledge of specific sequence information.

In sum, Nomoto does not teach or suggest examining the mitochondrial DNA to identify acquired germline mutations deriving from an ancestral cell, since the mutations that were specifically analysed by Nomoto were specific disease associated nucleotide substitutions, and are characteristic of one specific type of neoplasm and not any others. Further, Nomoto does not teach or suggest identifying the existence of a clonal population based on detecting co-localization, without the need to obtain specific sequence information.

Therefore, Greiner and Nomoto, taken alone or in combination, do not teach or suggest the invention as presently claimed. Accordingly, the rejection of Claims 14, 16, and 29 under 35 U.S.C. §103(a) as unpatentable over Greiner in view of Nomoto is overcome.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

Xiaochun Zhu
Registration No. 56,311

Scully, Scott, Murphy & Presser, P. C.
400 Garden City Plaza-STE 300
Garden City, New York 11530
Telephone: 516-742-4343
XZ:ab